# The Methacholine Challenge Test for Reversible Airways Disease Assessment: A Practical Guide on how to Interpret New 2017 ERS Guidelines

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## Summary

The assessment through a challenge test of severity of reversible broncho-constrictive disease, such as asthma, is an important part of the diagnosis process as well as defining treatment therapy. Methacholine is frequently used as the inhaled challenge substance and is given by inhalation via a nebulizer for a fixed exposure time to the methacholine concentration. The challenge test involves progressively increasing the concentration of methacholine and measuring the forced expiratory volume in 1 s ($FEV_1$) after exposure at each concentration level. The test is terminated after the first instance at which $FEV_1$ decreases by more than 20% from the pre-test reference value. New recommendations from the European Respiratory Society (ERS) have recommended basing the result upon the delivered dose (µg) of methacholine causing a 20% fall in $FEV_1$, termed the provocative dose ($PD_{20}$), rather than the former metric of methacholine concentration (mg/mL), causing the same fall in $FEV_1$ ($PC_{20}$). Given the detail and complexity of the recent guidance, we follow a step-wise approach to explain each stage of the new bronchial challenge test, then illustrate how $PD_{20}$ is calculated and used to interpret the degree of airway hyper-responsiveness. Although any nebulizer with validated methacholine delivery data could be used to deliver the agent, we illustrate how to apply the methodology, based on the same breath-actuated nebulizer (AeroEclipse-II* BAN) as was used, through references, in the new guidance.

## Introduction

The assessment through a challenge test of severity of reversible broncho-constrictive disease, such as asthma, is an important part of the diagnosis process as well as defining treatment therapy [1]. Methacholine is frequently used as the inhaled challenge substance, because the onset of symptoms upon inhalation of an appropriate concentration is rapid, and spontaneous recovery post-methacholine testing usually occurs within 45–60 min [2]. In practice, however, patients are usually given a bronchodilator at the end of testing to relieve challenge-induced bronchoconstriction more rapidly [2]. The bronchial challenge agent is given by inhalation via a nebulizer for a fixed exposure time to the concentration of methacholine. The provocation test involves progressively doubling the concentration of methacholine and measuring the forced expiratory volume in 1-s ($FEV_1$) after exposure at each concentration level. The test is terminated after the first instance at which $FEV_1$ decreases by more than 20% from the pre-test reference value.

New recommendations from an international European Respiratory Society task force have been published this year [3]. This technical standard, also endorsed by the American Thoracic Society, recommends basing the result of the bronchial challenge upon the delivered dose (mass expressed in µg) of methacholine causing a 20% fall in forced expiratory volume in 1 s ($FEV_1$). This is termed the provocative dose ($PD_{20}$), and replaces the former definition based on the provocative concentration of challenge agent resulting in a 20% reduction in $FEV_1$ ($PC_{20}$). This new end-point allows comparable results from either different aerosol delivery devices or protocols. Hence, the standard notes that any suitable nebuliser or dosimeter may be used, so long as the delivery characteristics are known [3].

It is recognized however that the change in approach to assess $PD_{20}$ rather than $PC_{20}$ has the potential to cause some confusion in how to execute the protocol in a practical manner. The purpose of the present interpretation is therefore to provide a simplified explanation with a practical, step-wise, example of how the test can be performed to meet the new standard.

## Bronchial Challenge Testing – Drug Delivery System

The new standard allows for 'any suitable nebulizer or dosimeter' but does require characterization of the device output and particle size to be demonstrated. The example provided in this abstract uses data from the breath actuated nebulizer (AeroEclipse-II* BAN, Trudell Medical International, London, Canada) that is specifically referenced in the new 2017 standard, using independently reported tidal breathing data (both *in vitro* and *in vivo*). Such a breath-actuated device, that only delivers the medication when the patient inhales, has the additional benefit of affording minimal exposure of health care personnel to fugitive emissions [4], although a filter can be placed on the expiratory limb to eliminate such exposure altogether [3]. At least two independent clinical studies have recommended using this breath actuated nebulizer for methacholine challenge testing [4, 5].

**How to perform the challenge test: Example calculation of $PD_{20}$**

1) Prepare the Methacholine Solutions for Challenge test

The dilutions of methacholine concentrate can be prepared in the same way as with the previous 1999 guidance, prior to performing the challenge test and measurements of $FEV_1$. Table 1 shows an example of a schedule, based on the guidance in the new ERS document[3].

**Table 1 - Methacholine Concentrate Dilution Schedule in Which the Challenge Agent Concentration is Increased Four-Fold for Each Exposure**

| Label Mass of Concentrate (mg) | Start with: | Normal Saline Added to Effect Dilution (mL) | Obtain Diluted Concentration ($C_{MC}$) (mg/mL) | Code Letter to Provide Order of Dilution (see second column) |
|---|---|---|---|---|
| 100 | 100 mg | + 6.25 | 16.0 | A |
| | 3-mL of A | + 9.0 | 4.0 | B |
| | 3-mL of B | + 9.0 | 1.0 | C |
| | 3-mL of C | + 9.0 | 0.25 | D |
| | 3-mL of D | + 9.0 | 0.0625 | E |
| | 3-mL of E | + 9.0 | 0.015625 | F |

2) Calculate the Delivered Doses at different Methacholine concentrations

In order to establish the delivered dose to the lungs ($\mathbf{DD_{MC}}$) during a defined delivery duration, several key parameters regarding the nebulizer's output characteristics need to be known. For example, Appendix D of the new ERS standard [3] provides the following information for the BAN:

- For 20 seconds of tidal breathing, the delivery rate ($\mathbf{R_{MC}}$) of methacholine at the mouthpiece of the high output device (BAN) is 2.70 mg/min for a solution concentration ($\mathbf{C_{MC}}$) of 16 mg/mL when operated from a 50-psi dry gas source.
- The fine droplet fraction (**FDF**), defined as those droplets less than 5 µm aerodynamic diameter, is reported from *in vitro* measurements of BAN-emitted droplets made by laser diffractometry as being 0.76 [3].

Hence the $\mathbf{DD_{MC}}$ for t(s) can be calculated as $\mathbf{DD_{MC} = R_{MC}}$ x **FDF** x (t/60), and in the example provided for 20 seconds with the 16mg/mL concentration, $DD_{MC}$ would therefore be:

- 2.70 mg/min X 0.76 X 20/60 = 680 µg

This can further be generalized for any MC concentration using 20 seconds tidal breathing with the BAN as:

$\mathbf{DD_{MC}}$ = [$\mathbf{C_{MC}}$/16 mg/ml] X 680 µg.

3) Perform the bronchial challenge test

Once the calculations of $DD_{MC}$ are completed for all the concentrations prepared as part of the test phase in Table 1, the measurement of $FEV_1$ can be conducted at increasing concentrations. Table 2 is an example of a bronchial challenge report taken from Appendix F of the ERS standard [3]. The $\mathbf{DD_{MC}}$ values in this case are based upon a 1 minute tidal breathing test duration as recommended in the standard.

The test begins with a 'Pre-Challenge' to confirm that the patient can perform acceptable and repeatable spirometry, and ensure they have sufficient airflow at baseline. Increasing amounts of $DD_{MC}$ are delivered until such time as $FEV_1$ has fallen >20% from the reference (baseline) condition. In this particular example, in Table 2, the test was terminated after exposure to 127 µg ($\mathbf{D_2}$) and the dose at the second to last exposure $\mathbf{D_1}$ is 31.8 µg.

**Table 2 - Example Bronchial Challenge Report**

| Time of exposure | Test Phase | $DD_{MC}$ (µg) (1 min tidal breathing) | $FEV_1$ (L) | $FEV_1$ (% of reference) | Change in $FEV_1$ (% pre-challenge value) |
|---|---|---|---|---|---|
| $T_0$ | Pre-challenge | N/A | 3.10 | N/A | N/A |
| $T_0$ + 10 min | Post diluent (reference condition) | N/A | 3.00 | 100 | N/A |
| $T_0$ + 15 min | 0.015625 mg/mL | 1.9 | 3.05 | 102 | -2 |
| $T_0$ + 20 min | 0.0625 mg/mL | 7.65 | 2.94 | 98 | 2 |
| $T_0$ + 25 min | 0.25 mg/mL | 31.8 | 2.62 | 87 | 13 |
| $T_0$ + 30 min | 1.0 mg/mL | 127 | 2.16 | 72 | 28 |
| $T_0$ + 45 min | After bronchodilator administration | N/A | 3.20 | 107 | -7 |

4) Determination of $PD_{20}$

The $PD_{20}$ calculation is shown below and is illustrated using the example data from Table 2 where $R_1$ and $R_2$ are the percentage decreases in $FEV_1$ for $D_1$ and $D_2$, respectively.

$$PD_{20} = antilog\left\{\log D_1 + \frac{(\log D_2 - \log D_1)(20 - R_1)}{(R_2 - R_1}\right\}$$

$$PD_{20} = antilog\left\{3.46 + \frac{(4.84 - 3.46)(20 - 13)}{(28 - 13}\right\}$$

Consequently, from this particular example above, the bronchial responsiveness ($PD_{20}$) is determined as 61 µg.

5) Assessment of Airway Hyper-Responsiveness (AHR)

The $PD_{20}$ value can then be used to interpret the degree of AHR using values from the ERS document[3] represented below in Table 3. Based on the given example, the patient would be considered to have Mild AHR.

**Table 3 - Categorization of AHR to $PD_{20}$ of Methacholine**

| **$PD_{20}$ (µg)** | **Interpretation** |
|---|---|
| >400 | Normal |
| 100–400 | Borderline AHR |
| 25–100 | Mild AHR |
| 6–25 | Moderate AHR |
| <6 | Marked AHR |

## Conclusions

The new ERS standard allows the use of a more appropriate $PD_{20}$ endpoint to assess airway hyper-responsiveness. The methacholine challenge test procedure, calculation and interpretation have been described in an attempt to provide a meaningful practical demonstration of how the new guideline could be put into practice clinically.

**References**

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